CAP REPORT

NUMBER 12

Drugs and the Third World:

Cyproheptadine Risks and Unethical Marketing in Malaysia

CONSUMERS' ASSOCIATION OF PENANG

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Cyproheptadine Risks and Unethical Marketing in Malaysia

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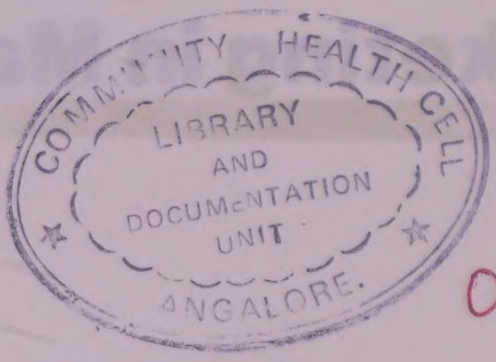

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PREFACE

Cyproheptadine, a potent antihistamine drug, is being promoted in Malaysia as an appetite stimulant for children. This is despite the fact that it has been reported that in children, some antihistamines can produce hallucinations, convulsions and even death.

In the US, there is only one drug preparation containing cyproheptadine, Periactin. It is indicated not as an appetite stimulant, but for use in allergy conditions and as a supporting drug in anaphylactic reactions. It is obvious that Merck Sharp and Dohme, the company producing this product, is practising double standards in its marketing of the product in developing countries.

In Malaysia, the *Drug Index for Malaysia and Singapore* lists six cyproheptadine preparations. All six are Group C Poisons. This means that they can be dispensed by a pharmacist with entry in the Prescription Book. However, some of the products have been obtained over the counter by CAP staff, without even an entry in the Prescription Book!

Developing countries which already have limited funds

available for the provision of adequate primary health care should not be spending money on unnecessary drugs.

We hope that this report will, to a certain extent, throw more light on the subject of the marketing of pharmaceutical drugs in developing countries like Malaysia.

It is also hoped that the Health Ministry will act fast to remove all preparations containing cyproheptadine on the market, and to put a ban on the drug.

S M Mohd Idris, JP
President
Consumers' Association of Penang
July 1986

Update

This report was presented to the Ministry of Health, Malaysia, in July 1986. On 5 October 1986, the Director of Health, Tan Sri Abdul Khalid, announced that cyproheptadine, together with six other drugs, has been banned in Malaysia. Manufacturers and distributors would be given three months' grace to withdraw all products containing cyproheptadine from the market.

CHAPTER 1

INTRODUCTION

Many dangerous pharmaceutical drugs which are banned or severely restricted in developed countries are still being widely marketed and used in developing countries. The drug cyproheptadine, which is a known potent anti-histamine drug, is being promoted as an appetite stimulant in Malaysia. Cyproheptadine has been proven to have many harmful side effects. Nevertheless it is still being promoted and marketed in Malaysia.

According to Professor Wong Hock Boon, head of the Department of Paediatrics, Faculty of Medicine, University of Singapore, the most important side effect of cyproheptadine is the possible one of interfering with the normal development of the brain during the critical period of the child's early development. If cyproheptadine is known to cause the above, why is it still being marketed as an appetite stimulant aimed specifically at children?

In a report which appeared in 1977 in the *Consumer Bulletin* published by the Consumers' Association of Singapore, Dr Matthew Gwee and Dr Yeoh said that the use of cyproheptadine as an appetite stimulant in children 'exposes the children

to unnecessary health hazards with negligible benefits. The use of cyproheptadine in an attempt to promote weight gain but at the risk of interfering with the normal mental and physical development of a growing child is totally irrational and dangerous'.

In the US, there is only one cyproheptadine preparation, called Periactin, which is indicated for use in allergy conditions and as a supporting drug in anaphylactic reactions after the acute manifestations have been controlled. The *Physicians' Desk Reference* does not indicate Periactin as an appetite stimulant. It is obvious that the marketing practices of the company producing this product are markedly different in developing countries.

In a press release published by Social Audit Limited dated 29 May 1986, it is stated that 'Experts describe appetite stimulant drug treatment as "appalling", "unethical", "contraindicated", "unjustified", "wrong" and "virtually never appropriate"'. However companies which produce these drugs - such as Merck Sharp and Dohme (USA) and Sandoz (Switzerland) - still claim their products 'have full regard to the needs of public health'.

In its campaign against inappropriate drug use, Social Audit, a UK public-interest group, has come up with a brochure in the form of a 'Dear Doctor' letter in which the views of over 80 Professors, most of them specialists in child health, are expressed. These experts agree almost unanimously that 'appetite stimulants have little if any

useful role in medicine'.

The following are some of the views expressed by some of the Professors interviewed.

One Professor of Child Health has the following to say: 'Wide advertisement and promotion of appetite stimulant drugs, particularly in the Third World where the basic requirement is food, strikes me and my colleagues as a particularly objectionable practice. I am not aware of any good evidence that appetite stimulant drugs confer any benefit in children with anorexia.'

According to a Professor of Clinical Pharmacology, 'There are almost no circumstances in which it would be appropriate to treat an anorexia child with appetite stimulant drugs. Anorexia is nearly always a sign of serious illness, which needs diagnosis and specific treatment ... I believe that the promotion of such drugs in the Third World is wrong.'

One Professor of Pharmacology says: 'Weight loss through either an inadequate food intake or imbalanced diet is not anorexia, and I can think of no circumstances in which either proper anorexia or diet-induced weight loss would benefit from treatment with an appetite stimulant drug. I would be hard put to describe any clinical circumstances that warrant treatment with an appetite stimulant acting on the central nervous system ... In fact, as a neuro-pharmacologist of over 25 years' standing, I have to say I am quite amazed (and appalled) that such substances as cyproheptadine and pizotifen are being "peddled" as appetite

stimulants.'

A Professor of Therapeutics and Clinical Pharmacology has the following view: 'The promotion of appetite stimulants for either children or adults is unjustified. That medication is so promoted to children in Third World countries is a manifestation of the competitive nature of the world's pharmaceutical industries. The advertising of such preparations is an exploitation of the naivity of the people in these countries, where very often there are very inadequate professional medical services available.'

According to a Professor of Paediatrics, 'It is never appropriate to treat anorexia in a child with appetite stimulant drugs. In my experience they simply do not work and anyway, the main reason for prescribing them is usually the demands of the parent, rather than the clinical situation of the child. I think they are a complete waste of time and money.'

Another Professor of Paediatrics has the following to say: 'Appetite stimulating drugs are virtually never appropriate in children. Having said that I will admit to having used Periactin occasionally, but really as a placebo and I will admit it represents a failure in my doctoring that I should have had to resort to it.'

Says Charles Medawar, Director of South Audit, 'Tens of millions of pounds a year are wasted on these products. On balance, these drugs do far more harm than good - and, on balance, the world would be better off without them.'

He added: 'Independent experts reckon that over half of all drugs on the world market are either not needed and/ or positively undesirable.' Appetite stimulants give clear evidence of this - and their sale and use on this scale is a disgrace.

This report by the Consumers' Association of Penang urges the Ministry of Health to immediately review the use of cyproheptadine and to impose a ban on its use. At present it is listed as a Group C Poison, which means that it can be dispensed by a pharmacist with entry in the Prescription Book. However, CAP staff have been able to purchase preparations containing this drug over the counter, without even so much as an entry in the Prescription Book!

CHAPTER 2

CYPROHEPTADINE: INN (International Nonproprietary Name Selected By WHO)

Cyproheptadine is one of the most potent of the antihistamine* drugs (*Martindale* 28th ed: 1298) which is also promoted as an appetite stimulant (Parish 1976: 328).

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* One of the chemicals mainly responsible for the body's allergic reactions is histamine. It is present in most tissues of the body and is released when cells are injured. The release of histamine may be caused by a physical process eg. sunburn, cold, light and friction as well as drugs. Antihistamine drugs block the effects of histamine. They may also reduce the intensity of allergic and anaphylactic (collapse of the circulation and fall in blood pressure) reactions. Antihistamines also affect the brain: in some people they can cause stimulation, but their usual effect is to depress the brain, leading to drowsiness and sleep. This depressing effect on the brain has meant that some antihistamines can be used to reduce motion sickness, and prevent nausea and vomiting due to pregnancy (Parish 1976: 120-121).

1) Uses of Antihistamines

Antihistamines relieve the symptoms of seasonal hay-fever (*Martindale* 28th ed: 1288) but have no effect upon the cause. Only about half the patients who suffer from perennial nasal congestion, running nose and sneezing (vasomotor rhinitis) respond to antihistamines (Ibid: 122).

Skin rashes like allergic nettle-rash (urticaria) respond well to antihistamines. They may be used to relieve itching; however there is a serious danger of producing allergic dermatitis when antihistamine preparations are applied to the skin. Given by mouth or injection, they relieve itching and swelling produced by insect bites.

Many drug reactions respond well to antihistamines, some of which are useful as sedatives (Ibid). Some antihistamines are effective in preventing motion sickness (Ibid).

Antihistamines are however of very doubtful and unproven value in cough medicines. In fact they may have undesirable effects because they dry the lining of the nose and respiratory tract, impairing natural defence systems. Apart from providing some relief from a running nose, they are of no benefit in treating the common cold (Ibid). Antihistamines are also useless in treating asthma, including allergic asthma (Ibid: 121). They may relieve allergic swelling of the face but are of little value if the swelling affects the throat and threatens life. They are also of little value in anaphylactic reactions (Ibid).

Antihistamines are of use in relieving the rash in serum sickness (an allergic reaction following the injection of a serum) and they are also useful in treating blood transfusion reactions (Ibid: 122).

Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (*Physicians' Desk Reference* 37th ed 1983: 1331).

2) Caution and Warnings

Antihistamines can enhance the sedative effect of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers (*Martindale* 28th ed: 1288). Some antihistamines have been reported to affect the metabolism of drugs in the liver (Ibid).

Overdosage of antihistamines, particularly in infants and children, may produce hallucinations, central nervous system depression, convulsions and death (*Physicians' Desk Reference* 37th ed 1983: 1331).

In children, these drugs may also diminish mental alertness; conversely, particularly in the young child, they may occasionally produce excitation. In elderly patients they can cause dizziness, sedation and hypotension (Ibid).

3) Actions

Cyproheptadine has an atropine-like action and should be used with caution in patients with a history of bronchial asthma, hyperthyroidism, cardiovascular disease, hypertension and increased intraocular pressure (Ibid).

The drug should not be taken if one is allergic to phenothiazine-type (tranquilliser) drugs such as chlorpromazine and prochlorperazine. Signs of allergies to these drugs include sore throat, fever, unusual bleeding or bruising, rash, blurred vision and yellowing of skin (Silverman 1976: 81).

The safe use of cyproheptadine in pregnancy has not been established and it can also inhibit lactation in nursing mothers (*Consumer Bulletin* April-June 1977: 6).

When taking this drug, patients should be warned about engaging in activities requiring mental alertness and motor coordination, such as driving a car or operating machinery (*Physicians' Desk Reference* 37th ed 1983: 1331).

Cyproheptadine has multiple neurochemical effects. Its potency as a serotonin antagonist and the likelihood that this property accounts for its therapeutic effect in Cushing's disease has led to speculation that this property accounts for its apparent antidepressant effect (Balsal, et al, 1983: 803).

4) Drug Interactions

Alcohol will increase the drowsiness or sleepiness produced by cyproheptadine. It can also influence the effectiveness of any high blood pressure medicine. An MAO (Monoamine oxidase) inhibitor can interact with cyproheptadine to prolong the drying effect of the antihistamine, causing dry mouth and blurred vision (Ibid: 81-82). It can produce specific adverse drug effects in people with Parkinson's disease (Ibid).

5) Adverse Side Effects

The most common is drowsiness. Others include inability to concentrate, dizziness, noise in the ears, lack of coordination, fatigue, blurred vision, double vision, changes of mood, nervousness, delusions, hallucinations, insomnia and tremors, nightmares, loss of appetite, dryness of the mouth, tightness of the chest, and tingling, heaviness, weakness of the hands, cough, frequency and difficulty in passing urine, urinary retention, early menses, palpitations and headache. It can cause gastro-intestinal disturbances like nausea, vomiting, diarrhoea or constipation, colic and epigastric pain (Parish 1976: 121 and *Martindale* 28th ed: 1287). Other side effects include photosensitivity, thrombocytopenia, anorexia and allergic manifestations of rash and edema (*Physicians' Desk Reference* 37th ed 1983: 1331).

In infants and children, some antihistamines act as cerebral stimulants and symptoms of overdosage may

include hallucinations, central nervous system depression, convulsions and death (Ibid).

Antihistamines can occasionally cause allergy and anaphylaxis (increased susceptibility to the action of a foreign protein as the result of a first injection of the substance) (*Martindale* 28th ed: 1287). Local application of antihistamines carries a great risk of skin sensitisation but skin reactions can also result from oral administration. Serious blood disorders including agranulocytosis and haemolytic anaemia have also been reported (Ibid).

There have been reports suggesting a possibility of human foetal abnormalities resulting from the use of antihistamines such as chlorcyclizine, cyclizine, and meclozine (Ibid). Cyproheptadine may also produce adverse effects common to the phenothiazine class of drugs, such as tremors, a spastic, uncontrollable motion, and (rarely) a form of jaundice (yellowing of the skin and eyes) (Silverman 1976: 81).

CHAPTER 3

STUDIES ON CYPROHEPTADINE

1) The Dangers of Cyproheptadine as an Appetite Stimulant

In a 1977 report in the *Consumer Bulletin* (April-June 1977) published by the Consumers' Association of Singapore, Dr Matthew Gwee and Dr Yeoh wrote that cyproheptadine (brand name Periactin) was a very popular appetite stimulant in Singapore. In their article, the doctors said that although the drug has definite appetite stimulant properties, this had been regarded by some medical authorities as rather unpredictable and unimpressive. According to a report the doctors had read, 'the dosage of cyproheptadine recommended for appetite stimulation in children causes a significant suppression of the release of growth hormone in humans'. This will eventually lead to an inhibition or stunting of growth in children. The long-term effect of the drug on the mental development of a growing child is still uncertain. In view of these dangers, they concluded that the use of cyproheptadine as an appetite stimulant in children 'exposes the children to unnecessary health hazards with negligible benefits.

The use of cyproheptadine in an attempt to promote weight gain but at the risk of interfering with the normal mental and physical development of a growing child is totally irrational and dangerous'.

The doctors also mentioned that another drug Pizotifen which was being used as an appetite stimulant in children should also be regarded in the same light.

According to Professor Wong Hock Boon, cyproheptadine 'acts on the appetite centre in the brain by interfering with the neural chemicals which are responsible for central nervous system function' (Wong 1977: 7). The drug is also responsible for some serious side effects on children but 'probably the most important side effect is the possible one of interfering with the normal development of the brain during this critical period of the child's early development' (Ibid).

Professor Wong also added that when the drug treatment is stopped, 'the appetite returns to its pre-treatment level and any weight gained is then lost' (Ibid). In his opinion, 'there is no justification in taking this drug to stimulate the appetite of a child, who is organically normal and healthy, as it exposes him to potential serious side effects' (Ibid).

In the US, there is only one cyproheptadine preparation marketed by Merck Sharp & Dohme, called Periactin. In the 1983 edition of the *Physicians' Desk Reference*, it is indicated for use in allergy conditions and as a

supporting drug in anaphylactic reactions, after the acute manifestations have been controlled. Periactin is not indicated as an appetite stimulant. Elsewhere, Periactin is recommended as an appetite stimulant.

2) Reports on the Effects of Cyproheptadine

i) Cyproheptadine induces remission in 30% to 50% of adults with Cushing's disease, usually within two to three months (Krieger 1983: 22). It is not clear whether early diagnosis increases the chances of successful treatment, because remissions and even shrinkage of pituitary tumours have been reported in patients with signs of advanced disease. Typically, relapse occurs after cessation of cyproheptadine therapy (Krieger, et al, 1975: 893) although prolonged remissions after treatment have occurred (Wiesen, et al, 1983: 436).

ii) Treatment of pregnant rats with cyproheptadine during the last eight days of gestation produced alterations in the function of the endocrine pancreas in the offspring. The abnormalities exhibited by 50-day-old progeny of drug-treated dams included glucose intolerance, a two-fold increase in levels of insulin in the pancreas, and an accentuated response to the insulin-lowering action of cyproheptadine in the endocrine pancreas. The alterations observed in these animals were limited to the insulin-containing cells, and no change was found in the pancreatic concentrations of glucagon and somatostatin. The results are the first

to demonstrate that post-natal pancreatic B-cell function can be selectively altered by prenatal exposure to an exogenous chemical (Chow, et al, 1984: 572-575).

3) *MIMS* Information

In the *Monthly Index of Medical Specialities (MIMS)* Australia (Oct-Nov 1979, V 16 No 6: 135) antihistamines are described in the following manner:

'USES: Allergic conditions such as hay fever, allergic rhinitus, urticaria and pruritus. Some eg. cyclizine, dimenhydrinate, diphenylpyraline, meclozine and promethazine are also useful in the treatment of motion sickness although it seems that they produce this effect by a central anticholinergic action rather than by blocking histamine receptors. Some with potent antiserotonergic activity eg. Cyproheptadine have also been used in the treatment of migraine.

SP/PREC: May produce drowsiness; may potentiate other CNS depressant compounds eg. alcohol, hypnotics, sedatives, tranquillisers; because of their anticholinergic activity they should be used with caution in conditions such as glaucoma; MAO inhibitors may prolong some of the actions; should be used with caution, if at all, in patients with epilepsy.

TOXIC EFFECTS: Mainly sedation, though CNS stimulation may occur at very large doses and children are susceptible to these stimulation. Other effects include g/i disturban-

ces, headache, dizziness, blood dyscrasias and anticholinergic effects such as dry mouth and blurred vision. Sensitisation may also occur following topical application.'

There are two cyproheptadine preparations listed, namely:

* Antegan Sr (Frosst), used in 'Allergic manifestations, migraine'

  and

* Periactin (Frosst), used in 'Allergy, pruritus, migraine'.

In *MIMS* UK (January 1980, V 22 No 1) there is one preparation containing cyproheptadine listed, namely Periactin, marketed by Merck Sharp and Dohme. It appears twice, under the Sections on 'Tonics; appetite stimulants' and 'Anti-allergic drugs'. Periactin is used for the 'Stimulation of appetite where increased food intake and weight gain are desirable'. Periactin is also available as 'yellow pineapple flavoured syrup'.

CHAPTER 4

REGULATIONS CONCERNING CYPROHEPTADINE

To date, only one country has taken action to ban this drug. In Bangladesh, under the provisions of the Drugs (Control) Ordinance, this product has been banned since it has been found to be an unncessary appetite stimulant, with serious side effects including visual hallucinations, photosensitivity, blurred vision and blood dyscrasias.

In Malaysia, under the Poisons Ordinance 1952 and the Poisons List 1983, cyproheptadine is listed as a Group C Poison. This means that it can be dispensed by a pharmacist with entry in the Prescription Book. Apart from this, there are no restrictions on the use of the drug.

CHAPTER 5

DRUG INFORMATION AND BRANDS SOLD IN MALAYSIA

In Malaysia, doctors obtain information on cyproheptadine from three major sources. They are:

a) The *Drug Index for Malaysia and Singapore (DIMS)*. *DIMS* is a quarterly publication on ethical medicines available in Malaysia and Singapore. It is prepared by the pharmaceutical companies and distributed free to doctors in both countries.

b) Drug advertisements and brochures which are distributed free to doctors by drug company detailmen.

c) Drug inserts which come together with the drugs when they are purchased. The insert gives information on the use of the drugs, the dangers and precautions to be taken when the drug is used. The instructions and information on the drug insert are provided by the company which markets its particular brand product.

1) *DIMS* Information

In Malaysia, *DIMS* (Vol 15 No 2 June 1986) lists six

cyproheptadine preparations. All six preparations are Group C Poisons which means that according to the law, they can be dispensed by a pharmacist with entry in the Prescription Book. However, CAP staff were able to purchase three of the preparations from pharmacies and drugstores without even so much as an entry in the Prescription Book.

The manufacturers of the various cyproheptadine preparations, together with their contents, are listed in Table I. From the table, it can be seen that the manufacturers are all foreign. Merck Sharp & Dohme markets three of its cyproheptadine preparations in Malaysia.

TABLE I: Cyproheptadine Preparations Available in Malaysia

Source: *DIMS* June 1986

	BRAND NAME	MANUFACTURER	CONTENTS
1.	Periactin	Merck Sharp & Dohme	Cyproheptadine HCL 4 mg
2.	Periactin-Vita	Merck Sharp & Dohme	Cyproheptadine 4 mg Vits. A, B1, B2, B6, B12, C, D

Periactin tablets, Periactin Vita tablets and Periactin-BC Syrup — all containing Cyproheptadine — which were bought over the counter by CAP staff.

	BRAND NAME	MANUFACTURER	CONTENTS (continued)	
3.	Periactin B-C	Merck Sharp & Dohme	Cyproheptadine HCL Vits. B complex and C	
4.	Cyprogin-vit	Atlantic Lab.	Cyproheptadine Vits. A, B1, B2, B6, B12, C, D, niacinamide	4 mg
5.	Cyprovit	Weber	Cyproheptadine Vits. A, B1, B2, B6, B12, C, D, niacinamide	4 mg
6.	Tres-Orix	Prodesfarma	Per 100 ml syrup: Cyproheptadine orolate Carnitine Lysine Vits. B1 B6 B12	 30 mg 3 mg 3 mg 200 mg 200 mg 2 mg
			Per capsule: Cyproheptadine orolate Carnitine Lysine Co-enzyme B12	 1.5 mg 150 mg 150 mg 1000 mg.

2) Warnings and Contraindications: Inadequate Information

Under the notes on 'Antihistamines' the special precautions indicated for the drug Periactin are as follows:

'May produce drowsiness; may impair ability to drive vehicles or operate machinery; may potentiate other CNS depressant compounds. Because of their anticholinergic activity, use with caution in conditions such as glaucoma. MAO inhibitors may prolong some of their actions. Large doses may precipitate fits in epileptics.'

Under indications is listed:

'Anti-allergic and anti-pruritic.
Treatment of bronchial asthma, migraine headache.'

Under contraindications the following is listed:

'Urinary retention. Pyloroduodenal obstruction, stenosing peptic ulcer. Elderly debilitated patients, nursing mothers, acute asthma attack. Concurrent administration of MAO inhibitors. Newborn and premature infants.'

Under the notes on cyproheptadine, the information on the brands, Periactin B-C and Periactin-Vita, is given in the following manner:

'Contra-Indications: Glaucoma, urinary retention, pyloroduodenal obstruction, stenosing peptic ulcer, symptomatic prostatic hypertrophy, bladder neck obstruction. Concurrent MAO inhibitor therapy; sensitivity to Cyproheptadine; elderly debilitated patients; acute asthma attack; nursing mothers; newborn or premature infants.

Special Precautions: Pregnancy; may produce drowsiness; may potentiate other CNS depressant compounds. Use with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease, or hypertension.'

The indications for the drugs Periactin B-C and Periactin-Vita are as follows:

* Periactin B-C
  Indications: Appetite stimulant.

* Periactin-Vita
  Indications: Appetite stimulant with vitamin supplementation.

It must be noted that despite the adverse effects and contraindications, cyproheptadine is still being used as an ingredient in preparations of appetite stimulants especially aimed at young children.

3) Brands Indicating Dosages for Children

There are three brands in *DIMS* indicating dosages for children. These are:

* Periactin Tablet 4 mg X 100's, 500's
  Periactin Syrup 2 mg/5 ml X 4 oz, 16 oz

  Dosage: Allergies, pruritus - children 2-6 years: 2 mg three times daily, total dosage is not to exceed 8 mg a day.

* Periactin B-C Syrup 2 mg/5 ml X 16 oz

Dosage: Children: 2-4 mg three times daily or four times daily depending on age and response.

* Tres-Orix Syrup 100 ml, and 250 ml
Capsule 20's, 1000's

Dosage: Children under 7 years: 1 tsp twice daily
Children 7 to 12 years: ½ tsp three times daily.

CHAPTER 6

DRUG INFORMATION INSERT AND BROCHURE

The drug insert for Periactin and the drug brochure for Periactin-Vita were examined. The drug insert recommended Periactin for a wide variety of ailments and many of the dangers of the drug were not sufficiently stressed. The drug brochure promoted Periactin-Vita as an appetite stimulant.

1) Drug Insert for Periactin (See Appendix 1)

In the drug insert, Periactin is described as 'the first clinically proven appetite stimulant ... it stimulates the appetite in a high proportion of children and in adults. Following discontinuation of therapy there may be some weight loss but usually not to pre-treatment levels'.

It is indicated 'as an appetite stimulant for those with decreased appetite or poor eating habits with resulting underweight, where stimulation of appetite, with weight gain is desirable'.

The dosage recommended 'for stimulation of appetite' in children is:

'2 to 6 years - dosage is not to exceed 8 mg per day.
7 to 14 years - dosage is not to exceed 12 mg per day'.

The maximum dosage for 'stimulation of appetite' for 2- to 6-year-olds is equal to the dosage recommended 'for allergies and pruritus' among the same age group.

2) Drug Brochure for Periactin-Vita (See Appendix 2)

In the drug brochure, Periactin-Vita Mineral is advertised as 'Good medicine to promote good nutrition'.

The brochure also quotes studies to show that 'Periactin Enhances Appetite'.

On the two-leaf brochure, there is a drawing of a young boy with a plate of food which is hardly eaten. He does not show any interest in the food either. On the other leaf, the same boy is in the football field standing next to a coach and looking very lethargic while his friends are vigorously playing in the background. The message put across is that Periactin will increase his appetite and make him strong, healthy and active.

From the above examples, we can see that Merck Sharp & Dohme, the US company which manufactures Periactin, maintains two standards for the drug it sells at home and that sold abroad. This constitutes irresponsible promotion and marketing. The Ministry of Health should immediately withhold the promotion and sale of the drug until proper labelling is carried out by the company.

The health of young consumers must be protected and doctors and parents must be warned of the dangers of prescribing this drug unnecessarily to children.

CHAPTER 7

CONCLUSION

This report has attempted to make a case for the need to remove all cyproheptadine preparations from the market. In so doing it has examined current studies on the drug in the medical literature; legislation and action taken by health authorities on the drug worldwide; and information and marketing of the drug in Malaysia.

Cyproheptadine is one of the most potent of the antihistamine drugs which are promoted as appetite stimulants. The side effects have been found to be dangerous to health. It would be relevant here to quote once more the views expressed by two doctors, Matthew Gwee and Yeoh, of the Consumers' Association of Singapore: The use of cyproheptadine as an appetite stimulant in children 'exposes the children to unnecessary health hazards with negligible benefits. The use of cyproheptadine in an attempt to promote weight gain but at the risk of interfering with the normal mental and physical development of a growing child is totally irrational and dangerous.' It would also be worthwhile to quote once more Professor Wong Hock Boon: 'Probably the most important side effect is

the possible one of interfering with the normal development of the brain during this critical period of the child's early development. There is no justification in taking this drug to stimulate the appetite of a child, who is organically normal and healthy, as it exposes him to potential serious side effects.'

CAP strongly urges the Ministry of Health to immediately recall the drug from the market for the safety and health of Malaysian consumers.

CAP would like to repeat its call for the setting up of an independent unit within the Ministry of Health to control and evaluate imported as well as locally manufactured drugs during all stages of manufacture, packing, storage, advertising and distribution of medicines. This body should comprise medical doctors, pharmacists and pharmacologists to look into all the aspects mentioned and to advise legislation along the lines of the Food and Drug Administration (USA), the Committee on Safety of Medicines (UK) and the Export Committee, Ministry of Health in Bangladesh.

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APPENDIX 1

DRUG INSERT FOR PERIACTIN

65993505 0

Tablets/Syrup

PERIACTIN*

(cyproheptadine hydrochloride, MSD)

PERIACTIN* (cyproheptadine hydrochloride, MSD) is the first clinically proven appetite stimulant. In recommended doses it stimulates the appetite in a high proportion of children and in adults. When food is freely available, appetite stimulation is usually accompanied by a gain of weight. The appetite stimulation effect and gain in body weight occur only during the period of drug administration. Following discontinuation of therapy there may be some weight loss but usually not to pre-treatment levels.

PERIACTIN is a serotonin and histamine antagonist and is also recommended for the treatment of allergic disorders and pruritic dermatoses. PERIACTIN is available as a tablet and as a syrup.

CLINICAL ADVANTAGES

As an appetite stimulant

- The first clinically proven appetite stimulant.
- Produces a specific, consistent reproducible effect on appetite in the majority of patients.
- Increased appetite—food intake—with weight gain as a natural consequence.
- Weight gain can usually be expected to begin after one week of therapy
  - without clinical evidence of fluid retention
  - without clinical evidence of disturbance of endocrine function.

As an antiallergic-antipruritic

- Offers comprehensive control of allergies and pruritic dermatoses.
- Provides prompt relief of whealing, itching and erythema...reduces the tendency to scratch...lessens risk of secondary infection.
- Well tolerated...no extrapyramidal effects.

INDICATIONS

As an appetite stimulant

PERIACTIN is recommended for those patients with decreased appetite or poor eating habits with resulting underweight, where stimulation of appetite, with weight gain, is desirable.

As an antiallergic-antipruritic

PERIACTIN has a wide range of antiallergic and antipruritic activity and can be used successfully in the treatment of acute and chronic allergies and pruritus, such as: dermatitis, including neurodermatitis and neurodermatitis circumscripta, eczema, eczematoid dermatitis, mild, local allergic reactions to insect bites, hay fever and other seasonal rhinitis, perennial allergic and vasomotor rhinitis, urticaria, angioneurotic edema, drug and serum reactions, anogenital pruritus and pruritus of chickenpox.

In asthma

PERIACTIN is sometimes helpful in bronchial asthma and is recommended for trial in all patients who cannot obtain relief from conventional asthma therapy. Some patients obtain rapid relief with low dosage, while others may have little or no relief with any dosage. Seasonal asthma usually responds more satisfactorily than intrinsic asthma. Because of possible drying effect on bronchial secretions PERIACTIN should be used with caution.

In migraine headache

PERIACTIN has been reported to have beneficial effects in 70 to 80 percent of patients diagnosed as having vascular types of headache, such as migraine and histamine cephalalgia. Many patients who have not been able to obtain adequate relief from any other agent have reported ameliora-

*Trademark.

continued next page

tion of symptoms with PERIACTIN. The characteristic headache and feeling of malaise may disappear within an hour or two after the first dose.

DOSAGE AND ADMINISTRATION

PERIACTIN is available in a tablet and syrup form.

Each 5 ml. of Syrup PERIACTIN contains 2 mg. of cyproheptadine hydrochloride; Tablets PERIACTIN contain 4 mg. of cyproheptadine hydrochloride.

There is no recommended dosage schedule for children under 2 years of age. PERIACTIN is not recommended for use in elderly debilitated patients.

For stimulation of appetite

Suggested dosage range: 6-16 mg./day (depending upon age and response of the patient).

Tablets: ½-1 tablet 3 or 4 times daily.

Syrup: 1-2 teaspoonfuls† 3 or 4 times a day.

Children

2 to 6 years—dosage is not to exceed 8 mg. per day.

7 to 14 years—dosage is not to exceed 12 mg. per day.

Adolescents and Adults

The optimum recommended dosage is 12 mg. per day.

For allergies and pruritus

Dosage must be individualized. Since the effect of a single dose usually lasts four to six hours, the daily requirement should be given in divided doses three times a day or as often as necessary to provide continuous relief.

Adults

The therapeutic range is from 4 mg. to 20 mg. a day, the majority of patients requiring 12 mg. to 16 mg. a day. An occasional patient may require as much as 32 mg. a day for adequate relief. It is suggested that dosage be initiated with 4 mg. (1 tablet or 2 teaspoonfuls) three times a day and adjusted according to the size and response of the patient. The dosage is not to exceed 32 mg. a day.

Children (6 to 14 years)

The usual dosage is 4 mg. (1 tablet or 2 teaspoonfuls) three times a day. This dosage may be adjusted as necessary according to the size and response of the patient. If an additional dose is required, it should be taken preferably at bedtime. The dosage is not to exceed 16 mg. a day.

Children (2 to 6 years)

It is suggested that dosage be initiated with 2 mg. (½ tablet or 1 teaspoonful) three times a day and adjusted as necessary according to the size and response of the patient. If an additional dose is required, it should be taken at bedtime. The total dosage is not to exceed 8 mg. a day.

For migraine and vascular type of headache

Prophylactically or therapeutically, the recommended dosage is one 4 mg. tablet initially, repeated in ½ hour if necessary; not to exceed 8 mg. (2 tablets or 4 teaspoonfuls) in a 4- to 6-hour period. Relief usually is obtained in responsive patients with 2 tablets and maintained with 4 mg. every 4 to 6 hours.

CONTRAINDICATIONS

Although peripheral anticholinergic effects are minimal with recommended doses, cyproheptadine hydrochloride is contraindicated—as are all anticholinergics—in glaucoma, predisposition to urinary retention, and in patients with stenosing peptic ulcer or pyloroduodenal obstruction.

It is also contraindicated with concurrent monoamine oxidase inhibitor therapy and in sensitivity to cyproheptadine.

This drug should not be prescribed for elderly debilitated patients.

In an acute asthmatic attack, cyproheptadine hydrochloride should not be used.

PRECAUTIONS

As with all medications this preparation should be kept out of reach of children.

Overdosage of antihistamines, particularly in infants and children, may produce convulsions and death.

Use in Pregnancy: The use of any drug in pregnancy, lactation, or in women of childbearing age requires that the potential benefits be weighed against its possible hazards to mother and child. Lactation may be inhibited.

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†One teaspoonful is assumed to be equivalent to 5 ml. Attention is called to the potential error in the use of

continued next page

household units. A teaspoon may hold from 4 ml. to 7 ml. It is recommended, therefore, that a medicinal spoon or calibrated medicine glass be used.

This drug may impair alertness in some patients. Operation of automobiles and other activities made hazardous by diminished alertness should be avoided.

Patients should be cautioned against the ingestion of alcohol and other central nervous system depressants.

Patients who present symptoms of severe loss of appetite, should be observed carefully to exclude any serious underlying pathology.

Rarely, prolonged therapy with antihistamines may cause blood dyscrasias, but none have been reported with PERIACTIN.

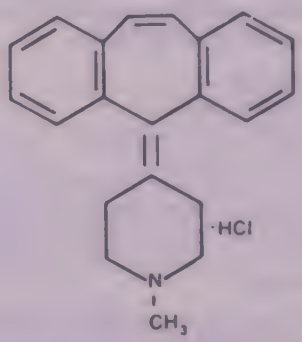
SIDE EFFECTS

The side effects that appear frequently are drowsiness and somnolence. In children drowsiness may be a desirable effect since it can decrease the emotional tension often associated with anorexia. Many patients who initially complain of drowsiness may no longer do so after the first three or four days of continuous administration. Drowsiness is often a desirable effect in patients with dermatitis and pruritus, since it tends to increase the threshold of perception and may decrease emotional tension caused by disease.

Dry mouth, dizziness, jitteriness, faintness, dryness of the mucous membranes, headache, nausea, and allergic skin manifestations or rash and edema have been reported in low incidence. Rarely, central nervous system stimulation (such as agitation, confusion, visual hallucinations) may occur.

CHEMISTRY

Cyproheptadine hydrochloride is a white to slightly yellowish crystalline solid soluble in water to the extent of about 4 mg. per ml. It is the sesquihydrate of 1-methyl-4-(5-dibenzo [a, e] cycloheptatrienylidene)-piperidine hydrochloride. The empirical formula is $C_{21}H_{21}N.HCl$ and the structural formula is:



PHARMACOLOGY

In laboratory animals cyproheptadine hydrochloride has been found to have appetite stimulation properties. Previous animal studies have also shown it to be an effective serotonin and histamine antagonist.

Cyproheptadine hydrochloride antagonizes the following effects of serotonin in laboratory animals:

- bronchoconstrictor (guinea pig)
- vasopressor (dog)
- spasmogenic (isolated rat uterus)
- edema (rat)
- lethal (*H. pertussis*-treated mouse)

In all these effects, cyproheptadine hydrochloride approaches, equals or surpasses the activity of specific serotonin antagonists, such as 1-benzyl-2-methyl-5-methoxytryptamine (BAS) and 1-benzyl-2-methyl-5-hydroxytryptamine (BMS). In contrast, specific antihistamines, even the most potent, show little or no serotonin antagonism. Thus, cyproheptadine hydrochloride must be considered a serotonin antagonist as well as a histamine antagonist.

Cyproheptadine hydrochloride antagonizes or blocks the following effects of histamine in laboratory animals:

- bronchoconstrictor (guinea pig)
- vasodepressor (dog)
- spasmogenic (isolated guinea pig ileum)
- anaphylactic shock, active and passive (guinea pig and mouse)
- increased gastric secretion (Heidenhain pouch dog)

That cyproheptadine hydro-

continued next page

chloride protects both guinea pigs and mice against **anaphylactic shock** is unusual. In guinea pigs, the pulmonary aspects of anaphylactic shock are attributable to the release of endogenous histamine and can be controlled by substances with specific antihistaminic activity. In mice, however, where histamine release seems to be less important and serotonin release may be involved, specific antihistamines are of little value in protecting against anaphylaxis. Thus, the protective effect of cyproheptadine hydrochloride in mice may be an antiserotonin effect.

The inhibitory effect of cyproheptadine hydrochloride in histamine-induced gastric secretion is also unusual because specific antihistamines do not influence this effect of histamine.

Because of its marked activity as an antagonist of serotonin and histamine in laboratory animals, cyproheptadine hydrochloride was evaluated in man in situations where standard antihistamines are not effective.

In one evaluation, skin reactions were induced in test subjects by the intradermal injection of histamine, serotonin, and histamine-releasing substances, such as Compound 48-80. The wheals and flares resulting from the injections were observed, as well as the degree of blueness of the wheals produced by intravenous injection of a protein dye, coomassie blue. Coomassie blue was used as an indicator of capillary leakage of plasma proteins because of its propensity for plasma binding and its safety for use in man. Cyproheptadine hydrochloride and two standard antihistamines were administered orally in moderate therapeutic doses. Only cyproheptadine hydrochloride led to a suppression of the whealing responses and the capillary damage demonstrated by the bluing reaction.

Acute and chronic toxicity studies in various laboratory animals indicate that cyproheptadine hydrochloride has an adequate margin of safety. In doses far greater than those in the therapeutic range, ataxia, sedation and tachycardia can be produced, but other objective signs of toxicity are not evident. There was no evidence of histomorphologic changes in the various organs when doses approximating sub-acute lethal doses were administered to dogs, monkeys, rabbits, and mice. Twelve months of oral toxicity studies in dogs did not reveal functional or anatomical changes. In chronic toxicity studies in rats, only at dosages (10 to 12 mg./kg./day) far in excess (approximately 200 times) of those required for pharmacodynamic effects, was reversible vacuolization of the beta cells of the pancreatic islets noted. This was not observed in the other four species of animals used in the toxicity studies. After six months of continuous drug administration there was no evidence of derangement of carbohydrate metabolism in man, as measured by serial blood sugar determinations and glucose tolerance tests.

Cyproheptadine hydrochloride has central nervous system effects in laboratory animals, including anticonvulsant and antitremor activity and behavioral effects. It has weak peripheral anticholinergic activity and moderate local anesthetic action. It exerts highly effective protection against burn shock in mice. Most of these properties are evident only with dose much larger than those used in therapy. In the rat, for instance, behavioral effects are produced only by doses 50 to 100 times greater than those required to produce antiserotonin activity.

AVAILABILITY

PERIACTIN tablets, each containing 4 mg. cyproheptadine hydrochloride, MSD in bottles of 50, 100, 250 and 500. PERIACTIN syrup, is supplied in bottles of 4 fl. oz. and 16 fl. oz. Each 5 c.c. contains 2 mg. cyproheptadine hydrochloride, 5% alcohol and 0.1% sorbic acid added as preservative.

MSD

MERCK SHARP & DOHME
(Australia) Pty. Limited, Granville, N.S.W.
Subsidiary of MERCK & CO., INC.
Rahway, N.J., U.S.A.

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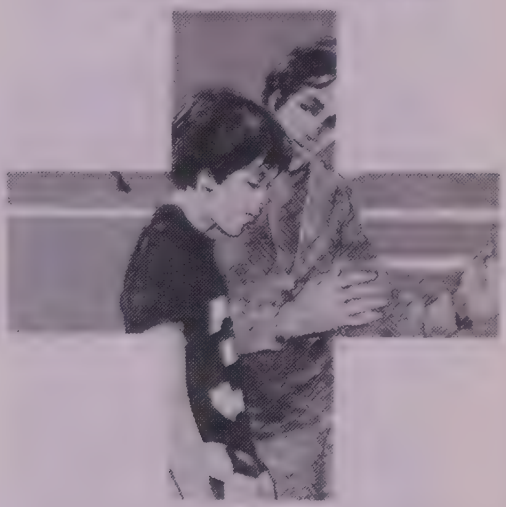
APPENDIX 2

DRUG BROCHURE FOR PERIACTIN-VITA

A UNIQUE AGENT TO
ENHANCE APPETITE

Good medicine to promote good nutrition



PLUS
14 VITAMINS AND MINERALS
TO SUPPLEMENT DIETARY
INADEQUACY

continued next page

Underweight adolescents are notorious for erratic eating habits, inadequate diet, and poor appetites. They often need just a little prompting to get them started.

A little help to get started

plus a balanced supplement of essential vitamins and minerals

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY CONFIRMS: PERIACTIN* (cyproheptadine HCl, MSD) ENHANCES APPETITE

Silbert[1] studied the effects of PERIACTIN vs. placebo in 81 male and female patients (ages 3-44, including 23 adolescents) with loss of appetite and low food intake from various causes. Treatment with PERIACTIN—at doses ranging from 2 mg. to 8 mg. —was given for three months.

Of his overall study, Silbert reported ...

"The results of this survey indicate that all treatment schedules were superior to placebos."[1]

Of his results in younger patients, Silbert reported ...

"[At] all PERIACTIN *doses [the treated groups] showed statistically significantly greater percentage increases in weight than the placebo group at weeks 8 and 12."*[1]

Beccari and Rondinini reported ...

"All of the children, from the first weeks of treatment, ate more and more readily, and accordingly showed good weight gain ..."[2]

1. Silbert, M.V.: The weight gain effect of PERIACTIN in anorexic patients, So. Afr. Med. J. 45:374-377, April 1971.

2. Beccari, A. and Rondinini, B.: Sperimentazione, su 40 bambini, della ciproeptadina come stimolante dell'appetito [Trial of cyproheptadine as an appetite stimulant in 40 children]. Minerva pediat. 23:345-347, February 1971.

*Trademark

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MOST PATIENTS GAIN WEIGHT

Numerous other studies have repeatedly demonstrated that PERIACTIN because of its effect on appetite produces significantly greater weight gains than placebo, in a high proportion of patients. Results can usually be observed after one week.

WEIGHT CAN BE MONITORED

The effect on appetite and resultant increase in patients' body weight occur *only* during the drug treatment period. Slight weight loss may follow discontinuance of therapy with PERIACTIN but usually not to pretreatment levels.

MINIMUM DAILY REQUIREMENTS SATISFIED

PERIACTIN-VITA MINERAL, when taken as recommended, will provide patients with minimum daily adult requirements of essential vitamins and minerals.

NO DISTURBANCE OF ENDOCRINE FUNCTION

PERIACTIN-VITA MINERAL contains no anabolic steroids or stimulants. PERIACTIN has not been reported to have any influence on the liver, premature epiphyseal closure, virilism, or fluid retention.

Transient drowsiness, sometimes noted during the first few days of therapy, is the most frequently reported side effect.

Good medicine to promote good nutrition

Not a tonic.
Not an anabolic steroid.

PERIACTIN-VITA Mineral

continued next page

Good medicine to promote good nutrition

Tablets Trademark

PERIACTIN-VITA Mineral

(cyproheptadine HCl with multivitamins and minerals)

PERIACTIN-VITA MINERAL is available for oral administration as a tablet, each of which provides the following:

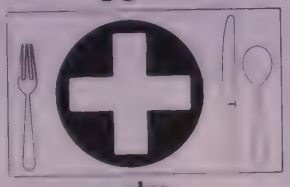
Cyproheptadine hydrochloride	4 mg.
Vitamin A	1333 I.U.
Vitamin D	133 I.U.
Thiamine mononitrate (B_1)	0.6 mg.
Riboflavin (B_2)	0.75 mg.
Pyridoxine hydrochloride (B_6)	0.6 mg.
Cyanocobalamin (B_{12})	2.5 mcg.
Niacinamide	5 mg.
Ascorbic acid (C)	20 mg.
Iron (as ferrous fumarate)	7.5 mg.
Copper (as the citrate)	0.5 mg.
Iodine (as sodium iodide)	0.12 mg.
Magnesium (as the oxide)	2.5 mg.
Manganese (as the carbonate)	0.5 mg.
Zinc (as the sulfate)	0.75 mg.

[NOTE: The amount of vitamins A and D to be filled in locally.]

DOSAGE:
Generally one tablet t.i.d. depending on age and response. If necessary, an additional tablet should be prescribed at bedtime. Children under six should not receive more than 2 tablets per day and there is no recommended dosage schedule for children under two years of age.

Please see the enclosed Physician's Direction Circular for detailed information on dosage, contraindications, precautions and side effects.

A unique agent to enhance appetite



plus
14 vitamins and minerals to supplement dietary inadequacy

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MERCK SHARP & DOHME

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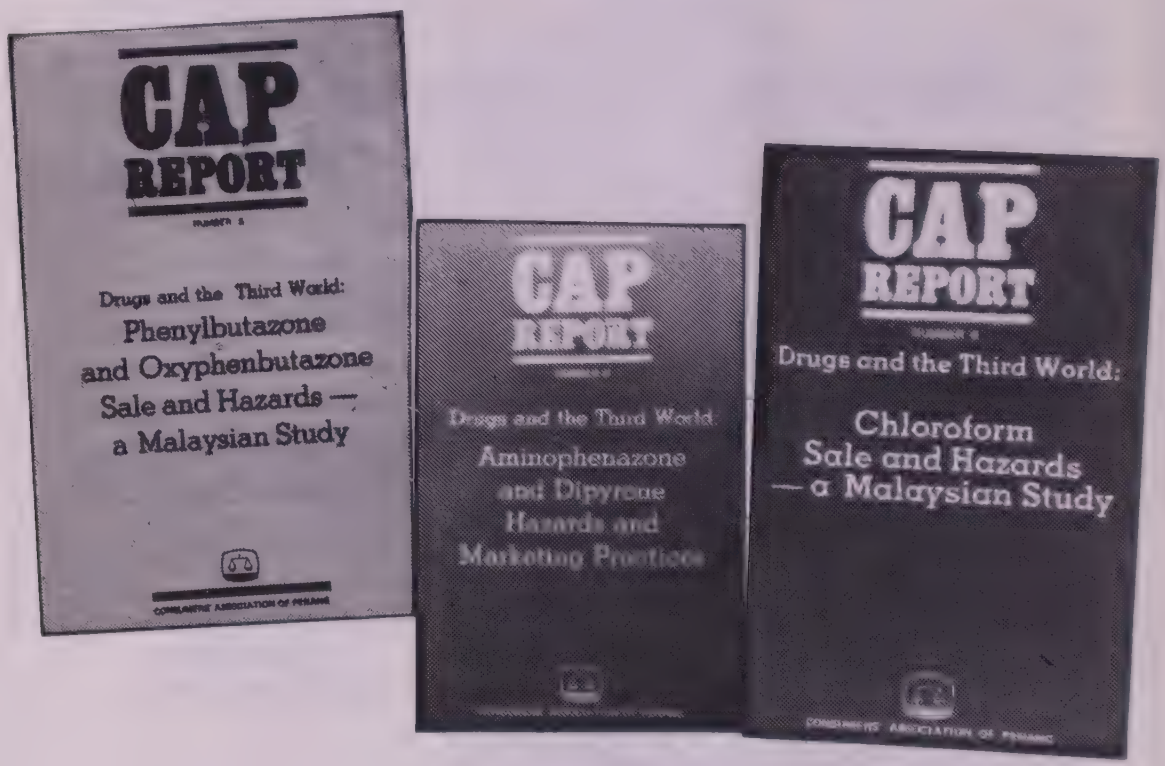

1)	* Oxyphenbutazone and Phenylbutazone	$5.00
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4)	* Phenacetin	
5)	* Pizotifen	
6)	* Stanozolol	

** Besides cyproheptadine, these drugs were also banned by the Malaysian government a few months after the reports were presented to the Ministry of Health.*

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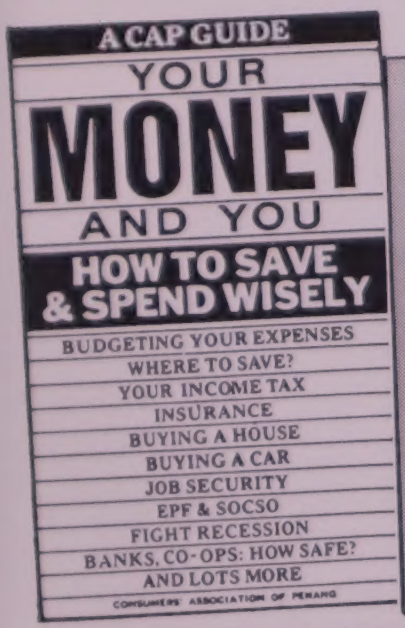

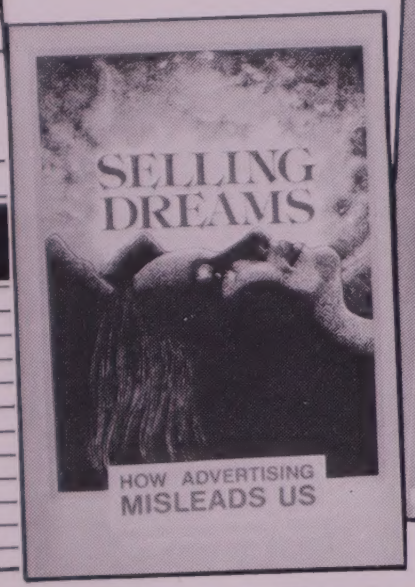

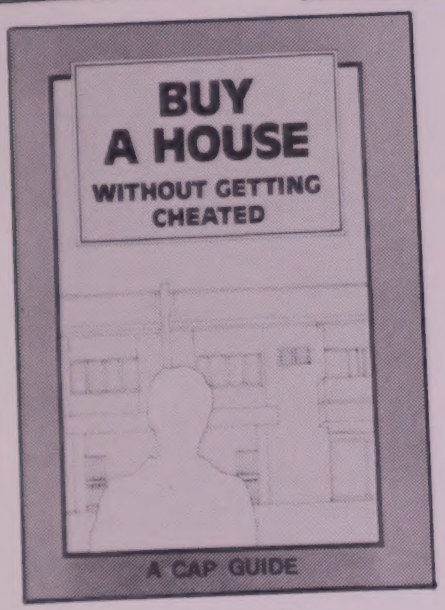

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Drugs and the Third World:

Cyproheptadine Risks and Unethical Marketing in Malaysia

Cyproheptadine is a potent antihistamine drug known to cause man harmful side effects. However, it is being promoted in Malaysia a an appetite stimulant for children.

In the US, cyproheptadine is not indicated as an appetite stimulan The drug is indicated for use in allergy conditions and as a supportin drug in anaphylactic reactions.

This report reveals the dangers of cyproheptadine to children, as we as the unethical marketing practices of the companies promoting th drug as an appetite stimulant in developing countries. The Ministr of Health is urged to remove all cyproheptadine preparations on sal in Malaysia, and ban the drug from further use.

In October 1986, a few months after CAP sent this report to th Malaysian Ministry of Health, the government banned the sale c cyproheptadine in Malaysia.

The Consumers' Association of Penang (CAP) is a non-profit making organis tion which fights for the rights and interests of Malaysian consumers throug research, educational and representational activities.

The issues it takes up include the fulfilment of basic needs (food, nutritio health, housing, transport, etc.), food and product safety, environmental poll tion and problems, the rational use of resources, specific problems of wome and business malpractices.

This is part of a series of CAP Reports aimed at providing the public with th results of some of the important areas of CAP's activities. It is hoped that th series will generate public interest and awareness, and help to contribute toward a better life for Malaysians.

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